UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/705,432 | 11/10/2003 | Wojtek Auerbach | REG 784 | 4884 |

26693 7590 08/28/2006

REGENERON PHARMACEUTICALS, INC
777 OLD SAW MILL RIVER ROAD
TARRYTOWN, NY 10591

| EXAMINER | |
|---|---|
| MONTANARI, DAVID A | |
| ART UNIT | PAPER NUMBER |
| 1632 | |

DATE MAILED: 08/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/705,432 | AUERBACH ET AL. | |
| | Examiner | Art Unit | |
| | David Montanari | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *31 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *17-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission fi led on 7/31/2006 has been entered.

2. The declaration by Dr. Frendewey has been considered.

*3.* Claims 17-32 are examined in the instant application.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 17-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rohozinski et al. (Genesis, 2002, Vol. 32, pgs. 1-7) in view of Tsirigotis et al. (BioTechniques, 2001, Vol. 31, pgs. 120-130) and Ghazizadeh et al. (J. Invest. Dermat., 1998 Vol. 111, pgs. 492-496).

Claims 17-32 are drawn to an *in vitro* method of targeting a targeting vector into mouse embryonic stem (ES) cell, comprising introducing into said ES cells a targeting vector comprising a ubiquitin promoter, wherein the targeting vector comprises a drug resistance gene

encoding neomycin phosphotransferase, hygromycin phosphotransferase, or puromycin acetyl transferase under control of a ubiquitin promoter, wherein said promoter is the ubiquitin C promoter that is a human, mouse, rat, or bacterial ubiquitin C promoter.

Rohozinski et al. teach a method of gene targeting in mouse ES cells via homologous recombination (pg. 1, Abstract). Rohozinski continues to teach that manipulating Y chromosome genes by homologous recombination in ES cells would be a direct way of addressing their function and testing the gene dosage hypothesis (pg. 1 col. 2 parag. 1 lines 1-4). Rohozinksi continues that successful targeting of the Y chromosome *Dby* and *Eif2s3y* genes using the disclosed method (pgs. 2-4). Rohozinksi does not teach the targeting of mouse ES cells with a targeting vector comprising the ubiquitin promoter.

Tsirigotis et al. teach that the ubiquitin promoter is one of the "best" promoters to achieve high levels of transgene expression in target cells (pg. 120 col. 3 last parag. bridge pg. 121 col. 1 lines 1-6). Tsirigotis continues to teach that transgenic mice were generated by microinjection of male pronuclei with an expression construct comprising the human ubiquitin C promoter and the GFP reporter gene as well as tested *in vitro* in HT4 murine neuroblastoma cells (pg. 121 col. 3 1$^{st}$ full parag.). Tsirigotis et al. continues to teach that said transgenic mice and cells resulted in uniform expression of GFP due the ubiquitous expression of the ubiquitin promoter (pg. 122 col. 2-3 bridge pg. 123). Tsirigotis does not teach a targeting vector in mouse ES cells.

Ghazizadeh et al. teach using a retrovirus vector comprising the lacZ gene and the neomycin phosphotransferase gene the to select non-transformed porcine keratinocytes using the drug G418 to select cells which are not expressing neomycin phosphotransferase (pg. 493, col. 1

parag. 3). Ghazizadeh does not teach a method of targeting a targeting vector into mouse ES cells.

Thus the ordinary artisan would have been motivated by the teachings of Rohozinski to modify the methods taught by Tsirigotis and Ghazizadeh to target specific chromosomal locations in mouse ES cell colonies exhibiting drug resistance by using any drug resistant gene as a selection agent. Motivation is provided by Rohozinski teaching that manipulating specific chromosomal genes is advantageous to study gene function. Further motivation is provided by Tsirigotis teaching that the ubiquitin promoter is one of the best promoters to use. Further motivation is provided by Ghazizadeh teaching that drug resistance genes are used to select cells that express the transgene of interest. Thus the cited art provides the requisite teachings and motivation to make and us the claimed invention.

***Response to Arguments***

Applicants argue in amendment filed 7/31/2006 the combined teachings of Rohozinski, Tsirigotis, and Ghazizadeh when combined do not teach nor motivate the ordinary artisan to make and use the claimed methods. Applicants submit a declaration by Dr. Frendewey which provides additional data comparing the targeting efficiency of the ubiquitin, PGK, and SV40 promoters. Applicants continue to argue that the novelty of the invention is the discovery that targeting efficiency in mouse ES cells is improved using the ubiquitin promoter. These arguments are not persuasive. The declaration and data provided has been considered, however these arguments do not overcome the 103(a) rejection. Applicants argue that targeting efficiency is significantly improved using the claimed method, and that the ordinary artisan would not have

been motivated at the time of filing to use the cited art of record to make and use the claimed method because it was not known at the time of filing that the targeting vector of the claimed method would be so efficient in targeting mouse ES cells. However, an examination of the art of record would have motivated the ordinary artisan to use the ubiquitin promoter in combination with targeting arms, and a resistance gene to target even mouse ES cells though they are not mentioned specifically. A targeting construct at its simplest form will target anything that has the appropriate arms for a desired region of DNA, whether it is in a mouse ES cell, or a HEPG2 cell etc. Thus for reasons of record discussed above and in previous office actions the rejection of claims 17-32 is maintained.

No claims are allowed.

## *Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Montanari whose telephone number is 1-571-272-3108. The examiner can normally be reached on M-F 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 1-571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

David A. Montanari, PhD

DAVE TRONG NGUYEN
SUPERVISORY PATENT EXAMINER